CHAPTER 93

Coating of Pharmaceutical Dosage Forms

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Any introduction to tablet coating must be prefaced by an important question—"Why coat tablets?"—since in many instances, the coating is being applied to a dosage form that already is functionally complete. In attempting to answer this question, if one examines the market, it will become apparent that a significant proportion of pharmaceutical solid dosage forms are coated. The reasons for this range from the esthetic to a desire to control the bioavailability of the drug, and include:

1. Protecting the drug from its surrounding environment (particularly air, moisture and light) with a view to improving stability.
2. Masking of unpleasant taste and odor.
3. Increasing the ease by means of which the product can be ingested by the patient.
4. Improving product identity, from the manufacturing plant, through intermediaries and to the patient.
5. Facilitating handling, particularly in high-speed packaging/filling lines, and automated counters in pharmacies, where the coating minimizes cross-contamination due to dust elimination.
6. Improving product appearance, particularly where there are noticeable visible differences in tablet core ingredients from batch to batch.
7. Reducing the risk of interaction between incompatible components. This would be achieved by using coated forms of one or more of the offending ingredients (particularly active compounds).
8. Improving product mechanical integrity, since coated products generally are more resistant to mishandling (abrasion, attrition, etc).
9. Modifying drug release, as in enteric-coated, repeat-action and sustained-release products.

Evolution of the Coating Process—Tablet coating is perhaps one of the oldest pharmaceutical processes still in existence. Although a great deal has been written about the materials and methods used, the coating process is still often recognized to be more of an art than a science, a factor which may be responsible for many of the problems that can exist. Historically, the literature cites Rhazes (850–932 AD) as being one of the earliest "tablet coaters," having used the mucilage of psyllium seeds to coat pills that had an offending taste. Subsequently, Avicenna[1] was reported to have used gold and silver for pill coating. Since then, there have been many references to the different materials used in "tablet coating." White[2] mentioned the use of finely divided talc in what was at one time popularly known as "pearl coating," while Kremers and Urdang[3] described the introduction of the gelatin coating of pills by Garot in 1838.

An interesting reference[4] reports the use of waxes to coat poison tablets. These waxes, being insoluble in all parts of the gastrointestinal tract, were intended to prevent accidental poisoning (the contents could be utilized by breaking the tablet prior to use).

While earlier coated products were produced by individuals working in pharmacies, particularly when extemporaneous compounding was the order of the day, that responsibility now has been assumed by the pharmaceutical industry. The earliest attempts to apply coatings to pills yielded variable results and usually required the handling of single pills. Such pills would have been mounted on a needle or held with a pair of forceps and literally dipped into the coating fluid, a procedure which would have to be repeated more than once to ensure that the pill was coated completely. Subsequently, the pills were held at the end of a suction tube, dipped and then the process repeated for the other side of the pill. Not surprisingly, these techniques often failed to produce a uniformly coated product.[5]

Initially, the first sugar-coated pills seen in the US were imported from France about 1842;[5] while Warner, a Philadelphia pharmacist, became among the first indigenous manufacturers in 1856.[6]

Pharmaceutical pan-coating processes are based on those used in the candy industry, where techniques were highly evolved, even in the Middle Ages. Today, while most coating pans are fabricated from stainless steel, early pans were made from copper, because drying was effected by means of an externally applied heat source. Current thinking, even with conventional pans, is to dry the coated tablets with a supply of heated air, and remove the moisture and dust-laden air from the vicinity of the pan by means of an air-extraction system.

Pan-coating processes underwent little further change until the late 1940s and early 1950s, with the conventional pan being the mainstay of all coating operations up to that time. However, in the last 20 or 30 years there have been some significant advances made in coating-process technology, mainly as a result of a steady evolution in pan design and its associated ancillary equipment.

Interestingly, in the early years of this development, an entirely new form of technology evolved, that of film coating. Recognizing the deficiencies of the sugar-coating process, advocates of film coating were achieving success by using coating systems involving highly volatile organic solvents. These circumvented the problems associated with the inefficiency in the drying capabilities of conventional equipment, and enabled production quotas to be met with significant reductions in processing times and materials used. The disadvantage of this approach, however, always has been associated with the solvent systems used, which often employed flammable and toxic materials.

The advances that occurred with equipment design, having begun by the development of the Wurster[7] process and continued by the evolution of side-vented pans, have resulted in the gradual emergence of coating processes where drying efficiency can be maximized. Thus, film coating began as a process using inefficient drying equipment, relying on highly volatile coating formulations for success, and evolved into one in which the processing equipment is a major factor in ensuring that rapid drying occurs. Improved drying capabilities have permitted increased use of aqueous film-coating formulations.

Advances in equipment design also have benefited the sugar-coating process, where, because of Current Good Manufacturing Practices (CGMP) and to maintain product uniformity and performance, the trend has been toward using fully automated processes. Nonetheless, film coating tends to dominate as the process of choice for tablet coating.

Pharmaceutical Coating Processes

Basically, there are four major techniques for applying coatings to pharmaceutical solid dosage forms: (1) sugar coat-

ing, (2) film coating, (3) microencapsulation and (4) compression coating.

Although it could be argued that the use of mucilage of psyllium seed, gelatin, etc, as already discussed, was an early form of film coating, *sugar coating* is regarded as the oldest method for tablet coating, and involves the deposition from aqueous solution of coatings based predominantly on sucrose as a raw material. The large quantities of coating material that are applied and the inherent skill often required of the operators combine to result in a long and tedious process.

Film coating, the deposition of a thin polymeric film onto the dosage form from solutions that were initially organic-solvent-based, but which now rely more and more on water as the prime solvent, has proven to be a popular alternative to sugar coating.

Microencapsulation is a modified form of film coating, differing only in the size of the particles to be coated and the methods by which this is accomplished. This process is based on either mechanical methods such as pan coating, air-suspension techniques, multiorifice centrifugal techniques and modified spray-drying techniques, or physicochemical ones involving coacervation-phase separation, where the material to be coated is suspended in a solution of the polymer. Phase separation is facilitated by the addition of a nonsolvent, incompatible polymer, inorganic salts or by altering the temperature of the system.

Compression coating incorporates the use of modified tableting machines which allow the compaction of a dry coating around the tablet core produced on the same machine. The main advantage of this type of coating is that it eliminates the use of any solvent, whether aqueous or organic in nature. However, this process is mechanically complex and has not proven popular as a method for coating tablets.

Sugar Coating of Compressed Tablets

While the term "sugar" is somewhat generic, and lends itself to describing various raw materials, sugar coating relies mainly on the use of sucrose. The main reason for this is that, based on the techniques involved, it is probably the only material which has enabled smooth, high-quality coatings to be produced, that are essentially dry and tack-free at the end of the process.

While the popularity of sugar coating has been on the decline, this process still retains some popularity, and many companies have invested in the complete modernization of the process.

In spite of certain inherent difficulties associated with the sugar-coating process, products which have been expertly sugar coated still remain among the most elegant available.

Since sugar coating is a multistep process, where esthetics of the final coated product is an important goal, it has been, and still is in many companies, highly dependent on the use of skilled manpower. For these reasons, the sugar-coating process is often protracted and tedious. However, processing times have been reduced gradually in the last two decades by the adoption of modern techniques and by the introduction of automation.

The sugar-coating process can be subdivided into six main steps: (1) sealing, (2) subcoating, (3) smoothing, (4) color coating, (5) polishing and (6) printing.

Sealing—The sealing coat is applied directly to the tablet core for the purpose of separating the tablet ingredients (primarily the drug) and water (which is a major constituent of the coating formulation) in order to assure good product stability. A secondary function is to strengthen the tablet core. Sealing coats usually consist of alcoholic solutions (approximately 10–30% solids) of resins such as shellac, zein, cellulose acetate phthalate or polyvinyl acetate phthalate. Historically, shellac has proven to be the most popular material although it can cause impaired bioavailability due to a change in resin properties on storage. A solution to this problem has been to use a shellac-based formulation containing a measured quantity of polyvinylpyrrolidone (PVP).[8]

The quantities of material applied as a sealing coat will depend primarily on the tablet and batch size. However, another important factor is tablet porosity, since highly porous tablets will tend to soak up the first application of solution, thus preventing it from spreading uniformly across the surface of every tablet in the batch. Thus, one or more further applications of resin solution may be necessary to ensure that the tablet cores are sealed effectively.

Since most sealing coats develop a degree of tack (stickiness) at some time during the drying process, it is usual to apply a dusting powder to prevent tablets from sticking together or to the pan. A common material used as a dusting powder is asbestos-free talc. Overzealous use of talc may cause problems, firstly, by imparting a high degree of slip to the tablets, thus preventing them from rolling properly in the pan, and secondly, presenting a surface at the beginning of the subcoating stage which is very difficult to wet, resulting in inadequate subcoat buildup, particularly on the edges. If there is a tendency for either of these problems to occur, one solution is to replace part or all of the talc with some other material such as terra alba, which will form a slightly rougher surface. Use of talc now is being frowned upon because of its potential carcinogenicity.

If an enteric-coated product is required, additional quantities of the seal-coat solution are applied. In this situation, however, it is preferable to use synthetic polymers such as polyvinyl acetate phthalate or cellulose acetate phthalate.

Subcoating—Subcoating is a critical operation in the sugar-coating process that can have a marked effect on ultimate tablet quality. Sugar coating is a process which often leads to a 50 to 100% weight increase, and it is at the subcoating stage that most of the buildup occurs.

Historically, subcoating has been achieved by the application of a gum-based solution to the sealed tablet cores, and once this solution has been distributed uniformly throughout the tablet mass, it is followed by a liberal dusting of powder, which serves to reduce tack and facilitate tablet buildup. This procedure of application of gum solution, spreading, dusting and drying is continued until the requisite buildup has been achieved. Thus, the subcoating is a sandwich of alternate layers of gum and powder. Some examples of binder solutions are shown in Table 1 and those of dusting powder formulations in Table 2.

While this approach has proved to be very effective, particularly where there is difficulty in covering edges. If care is not taken, a "lumpy" subcoat will be the result. Also, if the amount of dusting powder applied is not matched to the binding capacity of the gum solution, not only will the ultimate coating be brittle, but also dust will collect in the back of the pan, a factor which may contribute to excessive roughness.

An alternative approach which has proved popular, particularly when used in conjunction with an automated dosing system, is the application of a suspension subcoat formulation.

Table 1—Binder Solution Formulations for Subcoating

	A, % w/w	B, % w/w
Gelatin	3.3	6.0
Gum acacia (powdered)	8.7	8.0
Sucrose	55.3	45.0
Water	to 100.0	to 100.0

Table 2—Dusting Powder Formulations for Subcoating

	A, % w/w	B, % w/w
Calcium carbonate	40.0	—
Titanium dioxide	5.0	1.0
Talc (asbestos-free)	25.0	61.0
Sucrose (powdered)	28.0	38.0
Gum acacia (powdered)	2.0	—

In such a formulation the powdered materials responsible for coating buildup have been dispersed in a gum-based solution. A typical formulation is shown in Table 3. This approach allows the solids loading to be matched more closely to the binding capacity of the base solution, and often permits the less-experienced coater to achieve satisfactory results.

Smoothing—Depending on how successfully the subcoat was applied, it may be necessary to smooth out the tablet surface further prior to application of the color coating. Smoothing usually can be accomplished by the application of a simple syrup solution (approximately 60 to 70% sugar solids).

Often, the smoothing syrups contain a low percentage of titanium dioxide (1 to 5%) as an opacifier. This can be particularly useful when the subsequent color-coating formulation uses water-soluble dyes as colorants, since it makes the surface under the color coating more reflective, resulting in a brighter, cleaner final color.

Color Coating—This stage often is the most critical in the successful completion of a sugar-coating process, and involves the multiple application of syrup solutions (60 to 70% sugar solids) containing the requisite coloring matter. The types of coloring materials used can be divided into two categories: dyes or pigments. The distinction between the two simply is one of solubility in the coating fluid. Since water-soluble dyes behave entirely differently than water-insoluble pigments, the application procedure used in the color coating of tablets will depend on the type of colorant chosen.

When used by a skilled artisan, water-soluble dyes produce the most elegant of sugar-coated tablets, since it is possible to obtain a cleaner, brighter final color. However, since water-soluble dyes are migratory colorants (that is to say, moisture that is removed from the coating on drying will cause migration of the colorant, resulting in a nonuniform appearance), great care must be exercised in their use, particularly when dark shades are required. This can be achieved by applying small quantities of colored syrup that are just sufficient to wet the surface of every tablet in the batch, and then allowing the tablets to dry slowly. It is essential that each application is allowed to dry thoroughly before subsequent applications are made, otherwise moisture may become trapped in the coating and may cause the tablets to "sweat" on standing.

The final color obtained may result from up to 60 individual applications of colored syrup. This factor, combined with the need to dry each application slowly and thoroughly, results in very long processing times (eg, assuming 50 applications are made which take between 15 and 30 minutes each, the coloring process can extend over a period of up to 25 hours).

Tablet color coating with pigments, as advocated by Tucker *et al*,[9] can present some significant advantages. First of all, since pigment colors are water-insoluble, they present no problems of migration since the colorant remains where it is deposited. In addition, if the pigment is opaque, or is combined with an opacifier such as titanium dioxide, the desired color can be developed much more rapidly, thus resulting in a thinner color coat. Since each color-syrup application now can be dried more rapidly, fewer applications are required and significant reductions can be made in both processing times and costs.

Table 3—Typical Suspension Subcoating Formulation

	% w/w
Distilled water	25.0
Sucrose	40.0
Calcium carbonate	20.0
Talc (asbestos-free)	12.0
Gum acacia (powdered)	2.0
Titanium dioxide	1.0

Although pigment-based color coatings are by no means foolproof, they will permit more abuse than a dye color-coating approach, and are more amenable for use by less-skilled coaters. Pharmaceutically acceptable pigments can be classified either as inorganic pigments (eg, titanium dioxide, iron oxides) or certified lakes. Certified lakes are produced from water-soluble dyes by means of a process known as "laking," whereby the dye molecule becomes fixed to a suitable insoluble substrate such as aluminum hydroxide.

Certified lakes, particularly when used in conjunction with an opacifier such as titanium dioxide, provide an excellent means of coloring sugar coatings and permit a wide range of shades to be achieved. However, the incorporation of pigments into the syrup solution is not as easy as with water-soluble dyes, since it is necessary to ensure that the pigment is wetted completely and dispersed uniformly. Thus, the use of pigment color concentrates, which are commercially available, is usually beneficial.

Polishing—Sugar-coated tablets need to be polished in order to achieve a final gloss. Polishing is achieved by applying mixtures of waxes (beeswax, carnauba wax, candelila wax or hard paraffin wax) to the tablets in a polishing pan. Such wax mixtures may be applied as powders or as dispersions in various organic solvents.

Printing—In order to identify sugar-coated tablets (in addition to shape, size and color) often it is necessary to print them, either before or after polishing, using pharmaceutical branding inks, by means of the process of *offset rotogravure*.

Sugar-Coating Problems—Various problems may be encountered during the sugar coating of tablets. It must be remembered that any process in which tablets are kept tumbling constantly can present difficulties if the tablets are not strong enough to withstand the applied stress. Tablets which are too soft, or have a tendency to laminate, may break up and the fragments adhere to the surface of otherwise good tablets.

Sugar-coating pans exhibit inherently poor mixing characteristics. If care is not exercised during the application of the various coating fluids, nonuniform distribution of coating material can occur, resulting in an unacceptable range of sizes of finished tablets within the batch.

Overzealous use of dusting powders, particularly during the subcoating stage, may result in a coating being formed in which the quantity of fillers exceeds the binding capacity of the polymer used in the formulation, creating soft coatings or those with increased tendency to crack.

Irregularities in appearance are not uncommon, and occur either as the result of color migration during drying when water-soluble dyes are used, or of "washing back" when overdosing of colored syrups causes the previously dried coating layers to be redissolved. Rough tablet surfaces will produce a "marbled" appearance during polishing, since wax buildup occurs in the small depressions in the tablet surface.

Film Coating of Solid Dosage Forms

Film coating involves the deposition of a thin, but uniform, film onto the surface of the substrate. Unlike sugar coating, the flexibility afforded in film coating allows additional substrates, other than just compressed tablets, to be considered (eg, powder, granules, nonpareils, capsules). Coatings essentially are applied continuously to a moving bed of material, usually by means of a spray technique, although manual application procedures have been used.

Historically, film coating was introduced in the early 1950s in order to combat the shortcomings of the then predominant sugar-coating process. Film coating has proved successful as a result of the many advantages offered, including:

1. Minimal weight increase (typically 2 to 3% of tablet core weight).
2. Significant reduction in processing times.
3. Increased process efficiency and output.
4. Increased flexibility in formulations.
5. Improved resistance to chipping of the coating.

In the early years of film coating, the major process advantages resulted from the greater volatility of the organic solvents used. However, the use of such organic solvents has created many potential problems, including:

1. Flammability hazards.
2. Toxicity hazards.
3. Concerns over environmental pollution.
4. Cost (either relating to minimizing items 1–3, or to the cost of the solvents themselves).

However, since the initial introduction of film coating, significant advances have been made in process technology and equipment design. The emphasis has changed from needing highly volatile organic solvents (to achieve rapid drying), to attaining the same ultimate effect by designing equipment to have more efficient drying characteristics.

Thus, there has been a transition from conventional pans to side-vented pans and fluid-bed equipment, and consequently from the problematic organic solvent-based process to an aqueous one.

Film Coating Raw Materials—The major components in any film-coating formulation consist of a polymer, plasticizer, colorant and solvent (or vehicle).

Ideal properties for the polymer include solubility in a wide range of solvent systems to promote flexibility in formulation, an ability to produce coatings which have suitable mechanical properties and the appropriate solubility in gastrointestinal fluids such that drug bioavailability is not compromised.

Cellulose ethers are the preferred polymers in film coating, particularly hydroxypropyl methylcellulose. Suitable substitutes are hydroxypropyl cellulose, which may produce slightly tackier coatings, and methylcellulose, although this has been reported to retard drug dissolution.[10] Alternatives to the cellulose ethers are certain acrylics, such as methacrylate and methyl methacrylate copolymers.

Most polymers are employed as solutions in either aqueous or organic solvent-based systems. Alternative systems employ aqueous dispersions of water-insoluble polymers (eg ethylcellulose). Such systems usually are combined with aqueous solutions of water-soluble polymer in order to facilitate rapid drug release.

Many of the commonly used polymers are available in a range of molecular-weight grades, a factor which also must be considered in the selection process. Molecular weight may have an important influence on various properties of the coating system and its ultimate performance, such as solution viscosity and mechanical strength and flexibility of the resultant film.

The incorporation of a plasticizer into the formulation improves the flexibility of the coating, reduces the risk of the film cracking and possibly improves adhesion of the film to the substrate. To ensure that these benefits are achieved, the plasticizer must show a high degree of compatibility with the polymer, and be retained permanently in the film, if the properties of the coating are to remain consistent on storage. Examples of typical plasticizers include glycerin, propylene glycol, polyethylene glycols, triacetin, acetylated monoglyceride, citrate esters (eg, triethyl citrate) or phthalate esters (eg, diethyl phthalate).

Colorants usually are used to improve the appearance of the product as well as to facilitate product identification. Additionally, certain physical properties of the coating (eg its performance as a moisture barrier) may be improved. As in the case of sugar coating, colorants can be classified either as water-soluble dyes or insoluble pigments.

The use of water-soluble dyes is precluded with organic solvent-based film coating because of the lack of solubility in the solvent system. Thus, the use of pigments, particularly aluminum lakes, provides the most useful means of coloring film-coating systems. Although it may seem obvious to use water-soluble dyes in aqueous formulations, the use of pigments is preferred, since:

1. They are unlikely to interfere with bioavailability[11] as do some water-soluble dyes.
2. They help to reduce the permeability of the coating to moisture.[12]
3. They serve as bulking agents to increase the overall solids content in the coating dispersion.
4. They tend to be more light stable.

The major solvents used in film coating typically belong to one of these classes: alcohols, ketones, esters, chlorinated hydrocarbons and water. Solvents serve to perform an important function in the film-coating process, since they aid in the application of the coating to the surface of the substrate. Good interaction between solvent and polymer is necessary to ensure that optimal film properties are obtained when the coating dries. This initial interaction between solvent and polymer will yield maximum polymer-chain extension, producing films having the greatest cohesive strength and, thus, the best mechanical properties. An important function of the solvent systems also is to assure a controlled deposition of the polymer onto the surface of the substrate so that a coherent and adherent film coat is obtained.

Although it is very difficult to give typical examples of film-coating formulations, since these will depend on the properties of the materials used, such formulations usually are based on 5 to 15% (*w/w*) coating solids in the requisite vehicle (with the higher concentration range preferred for aqueous formulations), of which 60 to 70% is polymer, 6 to 7% is plasticizer and 20 to 30% is pigment.

Modified-Release Film Coatings

Film coatings can be applied to pharmaceutical products in order to modify drug release. The USP describes two types of modified-release dosage forms, namely those that are *delayed release* and those that are *extended release*. Delayed-release products often are designed to prevent drug release in the upper part of the gastrointestinal (GI) tract. Film coatings used to prepare this type of dosage form are commonly called *enteric coatings*. Extended-release products are designed to extend drug release over a period of time, a result which can be achieved by the application of a *sustained-* or *controlled-release* film coating.

Enteric Coatings—Enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents of the dosage form once it reaches the small intestine. The purpose of an enteric coating is to delay the release of drugs which are inactivated by the stomach contents, (eg, pancreatin, erythromycin) or may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids). In addition, such coatings can be used to give a simple repeat-action effect where additional drug that has been applied over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.

The action of enteric coatings results from a difference in composition of the respective gastric and intestinal environments in regard to pH and enzymatic properties. Although there have been repeated attempts to produce coatings which are subject to intestinal enzyme breakdown, this approach is not popular since enzymatic decomposition of the film is rather slow. Thus, most currently used enteric coatings are those which remain undissociated in the low pH environment of the stomach, but readily ionize when the pH rises to about 4 or 5. The most effective enteric polymers are polyacids having a pK_a of 3 to 5. Coatings subject to enzymatic breakdown are being considered now as protective coatings suitable for the colonic delivery of polypeptide drugs.

Historically, the earliest enteric coatings used formalin-treated gelatin, but this was unreliable since the polymerization of gelatin could not be controlled accurately, and often resulted in failure to release the drug, even in the lower intestinal tract. Another early candidate was shellac, but again the main disadvantage resulted from further polymerization that occurred on storage, often resulting in failure to release the active contents. Pharmaceutical formulators now prefer to use synthetic polymers to prepare more effective enteric coatings.

The most extensively used synthetic polymer is cellulose acetate phthalate (CAP) which is capable of functioning effectively as an enteric coating. However, a pH greater than 6 usually is required for solubility and thus a delay in drug release may ensue. It also is relatively permeable to moisture and gastric fluid compared to most enteric polymers. Thus it is susceptible to hydrolytic decomposition where phthalic and acetic acids are split off, resulting in a change in polymeric, and therefore enteric, properties.

Another useful polymer is polyvinyl acetate phthalate (PVAP) which is less permeable to moisture and gastric fluid, more stable to hydrolysis and able to ionize at a lower pH, resulting in earlier release of actives in the duodenum.

Other suitable enteric polymers include hydroxypropyl methylcellulose phthalate (which has properties similar to PVAP); methacrylic acid—methacrylic acid ester copolymers (some of which have a high dissociation constant[13]); cellulose acetate trimellitate (CAT, which has properties similar to CAP); carboxymethyl ethylcellulose (CMEC) and hydroxypropyl methylcellulose acetate succinate (HPMCAS).

Various systems recently have been introduced that allow many of these enteric polymers to be applied as aqueous dispersions, thus facilitating the use of aqueous film-coating technology for the enteric coating of pharmaceutical dosage forms.

Sustained-Release Coatings—The concept of sustained release formulations was developed in order to eliminate the need for multiple dosage regimens, particularly for those drugs requiring reasonably constant blood levels over a long period of time. In addition, it also has been adopted for those drugs which need to be administered in high doses, but where too rapid a release is likely to cause undesirable side effects (eg, the ulceration that occurs when potassium chloride is released rapidly in the gastrointestinal tract).

Formulation methods used to obtain the desired drug availability rate from sustained-action dosage forms include

1. Increasing the particle size of the drug.
2. Embedding the drug in a matrix.
3. Coating the drug or dosage form containing the drug.
4. Forming complexes of the drug with materials such as ion-exchange resins.

Only those methods which involve some form of coating fall within the scope of this chapter.

Materials which have been found suitable for producing sustained-release coatings include

1. Mixtures of waxes (beeswax, carnauba wax, etc) with glyceryl monostearate, stearic acid, palmitic acid, glyceryl monopalmitate and cetyl alcohol. These provide coatings which are dissolved slowly or broken down in the GI tract.
2. Shellac and zein—polymers which remain intact until the pH of gastrointestinal contents becomes less acidic.
3. Ethylcellulose, which provides a membrane around the dosage form and remains intact throughout the gastrointestinal tract. However, it does permit water to permeate the film, dissolve the drug and diffuse out again.
4. Acrylic resins, which behave similarly to ethylcellulose as a diffusion-controlled drug-release coating material.
5. Cellulose acetate (diacetate and triacetate).
6. Silicone elastomers.

As with an enteric coating, many of the synthetic polymers suitable for sustained-release film coating have been prepared as aqueous polymer dispersions (often called latexes or pseudolatexes) that are commercially available and facilitate the use of aqueous film-coating technology for the preparation of extended-release products.[14]

Various methods have been used to prepare sustained-release products using film-coating techniques. Examples include the application of suitable film coatings to

1. Dried granules (either irregular or spheronized).
2. Drug-loaded beads (or nonpareils).
3. Drug crystals.
4. Drug/ion-exchange-resin complexes.
5. Tablets.

In the first four examples, the final coated particles can either be filled into two-piece hard-gelatin capsules or compacted into tablets. Additionally, coated drug/ion-exchange-resin complexes may be dispersed in viscous liquids to create liquid suspensions.

A rather unique application of the film-coated, sustained-release tablet is the elementary osmotic pump. In this device, a tablet core (formulated to contain osmotically active ingredients) is film coated with a semipermeable membrane, which is subsequently "pierced" with a laser to create a delivery orifice. On the ingestion of such a device, the infusion of water generates an osmotic pressure within the coated tablet that "pumps" the drug in solution out through the orifice.

With sustained-release products, one must remain aware constantly of the fact that the final dosage forms typically contain drug loadings that are sufficiently high to cause problems if the entire dose is released quickly. This phenomenon, commonly called "dose-dumping," can be avoided only if:

1. The film coating is mechanically sound and will resist rupture on ingestion of the dosage form.
2. Sufficient coating is applied uniformly across the surface of the material that is to be coated.

Film-Coating Problems

As with sugar coating, difficulties may develop during, or subsequent to, the film-coating process. The tablets being coated may not be sufficiently robust, or may have a tendency to *laminate* while being coated. Since film coats are relatively thin, their ability to hide defects is significantly less than with sugar coating. Hence, tablets which have poor resistance to abrasion (ie, they exhibit high friability characteristics) can be problematic, since the imperfections readily may be apparent after coating. It is very important to identify tablets with suspect properties, whether mechanically or performance related (eg, poor dissolution), prior to a coating process, since subsequent recovery or reworking of tablets may be extremely difficult after a coating has been applied.

Various process-related problems can occur during the application of a film coating. One example is *picking*, which is a consequence of the fluid delivery rate exceeding the drying capacity of the process, causing tablets to stick together and subsequently become broken apart. Another example, *orange peel* or *roughness*, is usually the result of premature drying of atomized droplets of solution, or it may be a consequence of spraying too viscous a coating solution such that effective atomization is difficult.

Mottling, or lack of color uniformity, can result from uneven distribution of color in the coating, a problem often related to the use of soluble dyes in aqueous film coating, when color migration can occur, either by evolution of residual solvent in the film, or by migration of plasticizer in which the colorant may be soluble. The use of pigments in the film-coating process minimizes the incidence of this latter objection considerably. However, uneven color also can result from poor pigment dispersion in the coating solution.

Finally, some major problems occur as the result of internal stress that develops within the film as it dries. One example is *cracking*, which occurs when this stress exceeds the tensile strength of the film. This problem may be compounded by postcompaction stress relaxation (a phenomenon that can occur with certain types of tablet formulations, such as those containing ibuprofen, after ejection from the die), which causes tablets to expand. Another example is *logo-bridging* (ie, bridging of a monogram present in the surface of the tablet core), which occurs when a component of the internal stress is able to overcome the adhesive bonds between the coating and the tablet surface, causing the film to pull away so that legibility of the monogram is lost. An understanding of the properties of the various ingredients used in the film-coating formulation, and how these ingredients interact with one another, can allow the formulator to avoid many of these internal-stress-related problems.[15]

standpoint, coated tablets must be shown to conform, where applicable, to some color standard, otherwise the dispenser and the consumer may assume that differences have occurred from previous lots, signifying a changed or substandard product. In addition, because of the physical abuse that tablets, both in their uncoated and coated forms, receive during the coating process, it is essential to check for defects such as chipped edges, picking, etc, and ensure they do not exceed predetermined limits.

Often, in order to identify the products, coated tablets may be imprinted (particularly with sugar-coated tablets) or bear a monogram (commonly seen with tablets that are film-coated). The clarity and quality of such identifying features must be assessed. The failure of a batch of coated tablets to comply with such preset standards may result in 100% inspection being required or the need for the batch to be reworked.

Batch-to-batch reproducibility for drug availability is of paramount importance, consequently each batch of product should be submitted to some meaningful test such as a dissolution test. Depending on the characteristics of the tablet core to be coated, tablet coatings can modify the drug-release profile, even when not intended (unlike the case of enteric- or controlled-release products). Since this behavior may vary with each batch coated (being dependent, for example, on differences in processing conditions or variability in raw materials used), it is essential that this parameter should be assessed, particularly in products that are typically borderline (refer to Chapter 92).

Stability Testing of Coated Products

The stability-testing program for coated products will vary depending on the dosage form and its composition. Many stability-testing programs are based on studies which have disclosed the conditions a product may encounter prior to end use. Such conditions usually are referred to as normal and include ranges in temperature, humidity, light and handling conditions.

Limits of acceptability are established for each product for qualities such as color, appearance, availability of drug for absorption and drug content. The time over which the product retains specified properties, when tested at normal conditions, may be defined as the *shelf-life*. The container for the product may be designed to improve the shelf-life. For example, if the color in the coating is light-sensitive, the product may be packaged in an amber bottle and/or protected from light by using a paper carton. When the coating is friable, resilient material such as cotton may be incorporated in both the top and bottom of the container, and if the product is affected adversely by moisture, a moisture-resistant closure may be used and/or a desiccant may be placed in the package. The shelf-life of the product is determined in the commercial package tested under normal conditions.

The stability of the product also may be tested under exaggerated conditions. This usually is done for the purpose of accelerating changes so that an extrapolation can be made early, concerning the shelf-life of the product. Although useful, highly exaggerated conditions of storage can supply misleading data for coated dosage forms. Any change in drug release from the dosage form is measured *in vitro*, but an *in vivo* measurement should be used to confirm that drug availability remains within specified limits over its stated shelf-life. This confirmation can be obtained by testing the product initially for *in vivo* availability and then repeating at intervals during storage at normal conditions for its estimated shelf-life (or longer).

Interpretation of stability data for coated, modified-release products should be undertaken with extreme care, since the diffusion characteristics of polymeric films can change significantly under exaggerated temperature conditions. This change may be confounding when trying to predict their diffusion characteristics under more moderate conditions and thus can prove misleading when predicting shelf life.

When elevated-temperature stability studies are conducted on products coated with aqueous polymeric dispersions (latexes or pseudolatexes), the data obtained might be more indicative of morphological changes that have occurred in the film. Such changes may result from partial destruction of the film when coated material adheres together in the container and subsequently is broken apart; additionally, these changes might result from further coalescence of the coating (which can occur when the coating is not coalesced completely during the coating process).

Stability tests usually are conducted on a product at the time of development, during the pilot phase and on representative lots of the commercial product. Stability testing must continue for the commercial product as long as it remains on the market because subtle changes in a manufacturing process and/or a raw material can have an impact on the shelf life of a product.

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